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Risk of prostate cancer and family history of cancer: a population-based study in China

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We evaluated prostate cancer risk and family history of cancers using data from a case–control study in China. Cancer information among first-degree relatives was collected from 709 subjects (238 cases and 471 controls). None of the subjects reported a family history of prostate cancer. However, excess prostate cancer risk was associated with a family history of any cancer (OR = 1.79, 95% CI: 1.21–2.63) and esophageal cancer (OR = 2.39, 95% CI: 1.15–5.00). Nonsignificant risk was seen for family history of cancers of the stomach, lung, and female breast. Our results did not confirm the familial tendency toward prostate cancer but other cancers prevalent in China appeared to be aggregate, particularly esophageal cancer. Larger studies are needed to confirm these findings, and to clarify the genetic and lifestyle factors that may be involved.
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Introduction

Prostate cancer is a disease with marked international variation.[1–3] The incidence rate of clinical prostate cancer in African American men is 50 times higher than that in Chinese men.[1] Although Shanghai has one of the lowest reported incidence rates in the world (2/100 000 person-years), its incidence has increased by 70% from 1.63/100 000 in 1972–1977 to 2.78/100 000 in 1990–1994.[4] Age, race, and a family history of prostate cancer are the only established risk factors for prostate cancer.[5–9] Among Western men, first-degree relatives of prostate cancer patients have a 3- to 5-fold increased risk compared with the general population.[6–11] Less consistent is the risk of prostate cancer in relation to family history of other cancers, although some studies have suggested an excess risk associated with cancers of the stomach,[12,13] female breast,[10,14] and colorectum in close relatives.[15,16] As part of a population-based case–control study in Shanghai, China, we examined the association between a family history of cancer and clinical prostate cancer risk.

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Material and methods

Study population

Details of the study have been described previously.[17–20] Briefly, a total of 268 cases of primary prostate cancer (ICD-9, 185) newly diagnosed between 1993 and 1995 were identified through a rapid-reporting system established between the Shanghai Cancer Institute and 28 collaborating hospitals in urban Shanghai. Cases were permanent residents in 10 urban districts of Shanghai (henceforth, referred to as Shanghai) who did not have a history of any other cancer. For cancer cases, a standard medical abstract was used to collect information on date and method of diagnosis. The case ascertainment rate in the study was estimated to be greater than 95%, based on incidence data reported to the Shanghai Cancer Registry.

Information on potential controls was obtained from the personal identification cards maintained at the Shanghai Resident Registry, which contains personal registry cards for all adult residents (>18 y of age) in urban Shanghai. The cards contain name, address, date of birth, gender, and other demographic factors. Those who were deceased, had a history of cancer, or had moved out of the area before the sampling of controls were not eligible for the study. A total of 495 controls were selected randomly from among permanent residents of Shanghai (6.5 million) and frequency-matched to the age distribution (in 5-y age categories) of prostate cancer cases. Study staff visited the home of each selected control to verify eligibility for the study. In all, 471 eligible controls completed the interview (95%). Digital rectal examination (DRE) and prostate-specific antigen (PSA) testing were used to identify prostate-related disorders. Serum PSA levels were measured by Dianon Systems, Inc. (Stratford, CT, USA), by the PSA immunoassay, performed on the TOSOH AIA-1200 automated immunoassay instrument (Dianon Systems, Inc.).

Interview

In-person interviews were conducted to collect information on demographic characteristics, diet, tobacco smoking history, consumption of alcohol and other beverages, medical history, sexual behavior, and family history of cancers at various anatomic sites among first-degree relatives. Cases were interviewed at the hospital, whereas population controls were interviewed at home. Of the 268 eligible cases, 243 (91%) were interviewed. On average, cancer cases were interviewed within 20 days of diagnosis. Of the 495 eligible controls, 471 (95%) were interviewed.

Family history

The family history of cancers at various sites was determined by asking the subjects whether their first-degree relatives (including parents, siblings, and offspring) had been diagnosed with particular cancers. A person is defined as having a family history of a specific cancer if at least one first-degree relative was diagnosed with that cancer. Information on age at diagnosis of cancers was not available for the affected relatives.

Pathology review

To confirm the diagnoses of prostate cancer, an expert pathology panel (consisting of four study pathologists) from Shanghai first reviewed the pathology slides of the cases. The same slides were reviewed again by two independent pathologists from the US Armed Forces Institute of Pathology, and a consensus review was held with the Shanghai pathologist to confirm the diagnosis. After the consensus review, five cancer cases were determined to have benign prostatic hyperplasia and were excluded from the study, leaving 238 cases for analysis.

Statistical analyses

Statistical analyses were carried out using SAS version 6.12.[21] The distribution of variables such as age, education, province of origin, history of vasectomy or circumcision, number of relatives with cancer, and total number of relatives was examined for cases and controls. χ^2 tests were performed to determine the statistical significance of differences of these variables between cases and controls. Unconditional logistic regression models were used to estimate ORs and their corresponding 95% CIs for prostate cancer in relation to family history of cancers overall and at individual sites, including the female breast, stomach, esophagus, colorectum, liver, intrahepatic bile duct, uterus, and lung. Potential confounders such as age at interview, educational level, and sexual behavior were controlled for in the multivariate analyses. All statistical tests were two-sided.

Results

Selected characteristics of cases and controls are shown in Table 1. Age at diagnosis ranged from 50 to 94 y (median 73 y) for cancer cases. Cases and controls had a nearly equal number of first-degree relatives (mean 9.5 *vs* 9.1, median 9 for both) and a similar prevalence of vasectomy and circumcision. Compared with controls, cases had a slightly higher level of education, were less likely to be married, and were less likely to smoke or drink alcohol.

In total, 709 subjects reported having a total of 6557 first-degree relatives. A total of 99 (4.4%) and 120 (2.8%) relatives of case and control subjects, respectively, were reported to have had a diagnosis of cancer. Most common were cancers of the stomach ($n = 41$), esophagus ($n = 38$), and lung ($n = 30$). None of the subjects reported a family history of prostate cancer. However, excess prostate cancer risk was associated with a family history of any cancer (OR = 1.79, 95% CI: 1.21–2.63) or digestive tract cancer (OR = 1.84, 95% CI: 1.15–2.93) (Table 2). Among specific sites, a family history of esophageal

Table 1 Distribution of selected variables among cancer cases and population controls

Variables	Cases	Controls
Number	238	471
Mean age (median)	72.3 (73)	72.3 (73)
Average number of first-degree relatives (median)	9.5 (9)	9.1 (9)
Siblings	3.5	3.1
Offspring	4	4
Total number of first-degree relatives	2257	4300
Father	238	471
Mother	238	471
Brother	425	776
Sister	407	695
Son	495	976
Daughter	454	911
Numbers of relatives diagnosed with cancer	99	120
Vasectomy (%)	2.5	2.5
Average number of years of education	2.1	1.8
Circumcision (%)	2.9	3
Marital status (%)		
Married	90	93
Widowed/never married	10	7
Alcohol drinking (%)	32	42.8
Tobacco smoking (%)	53.9	66

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) for prostate cancer in relation to family history of cancers at specific sites

Family history of malignancy	First-degree relatives			Parents			Siblings			Offspring		
	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)
All cancers combined												
No	180	399	1	180	399	1	180	399	1	180	399	1
Yes	58	72	1.79 (1.21, 2.63)	32	32	2.21 (1.31, 3.73)	30	36	1.85 (1.10, 3.10)	5	9	1.20 (0.40, 3.64)
Digestive tract cancer												
No	180	399	1	180	399	1	180	399	1	180	399	1
Yes	38	46	1.84 (1.15, 2.93)	22	21	2.35 (1.25, 4.40)	17	22	1.71 (0.88, 3.29)	3	4	1.58 (0.35, 7.17)
Esophagus												
No	222	457	1	222	457	1	222	457	1	222	457	1
Yes	16	14	2.35 (1.13, 4.91)	10	7	2.94 (1.11, 7.83)	7	6	2.40 (0.80, 7.23)	0	1	—
			2.39 (1.15, 5.00)[a]									
Stomach												
No	221	451	1	221	451	1	221	451	1	221	451	1
Yes	17	20	1.74 (0.89, 3.38)	7	10	1.43 (0.54, 3.80)	9	11	1.67 (0.68, 4.09)	1	0	—
			1.72 (0.88, 3.35)[a]									
Liver, intra-hepatic bile duct												
No	233	463	1	233	463	1	233	463	1	233	463	1
Yes	5	8	1.24 (0.40, 3.84)	3	2	2.98 (0.50, 17.96)	1	4	0.50 (0.06, 4.47)	1	2	0.99 (0.09, 11.01)
			1.23 (0.40, 3.85)[a]									
Rectum												
No	233	467	1	233	467	1	233	467	1	233	467	1
Yes	5	4	2.51 (0.67, 9.42)	2	2	2.00 (0.28, 14.32)	2	1	4.01 (0.36, 44.44)	1	1	2.00 (0.13, 32.19)
			2.54 (0.67, 9.55)[a]									
Trachea, bronchus, and lung												
No	224	457	1	224	457	1	224	457	1	224	457	1
Yes	14	14	2.04 (0.96, 4.35)	5	5	2.04 (0.59, 7.12)	9	9	2.04 (0.80, 5.21)	0	1	—
			2.03 (0.95, 4.33)[a]									
Female tumors (ovary, breast, endometrium)												
No	180	399	1	180	399	1	180	399	1	180	399	1
Yes	15	17	1.98 (0.96, 4.08)	7	6	2.68 (0.88, 8.15)	6	7	1.90 (0.62, 5.82)	2	4	1.11 (0.20, 6.10)
Female breast												
No	230	463	1	230	463	1	230	463	1	230	463	1
Yes	8	8	2.01 (0.75, 5.43)	2	2	2.01 (0.28, 14.38)	4	2	4.03 (0.73, 22.14)	2	4	1.01 (0.18, 5.54)
			2.04 (0.75, 5.51)[a]									
Uterus												
No	231	463	1	231	463	1	231	463	1	231	463	1
Yes	7	8	1.75 (0.63, 4.90)	5	4	2.51 (0.67, 9.42)	2	4	1.00 (0.18, 5.51)	0	0	—
			1.79 (0.64, 5.02)[a]									

[a]Multivariate odds ratios when age and vasectomy history were adjusted.

Table 3 Odds ratios (ORs) and 95% confidence intervals (CIs) for prostate cancer by age at diagnosis in relation to family history of malignancies at specific sites

Family history of malignancy involved	72 y			>72 y		
	Case	Control	OR (95% CI)	Case	Control	OR (95% CI)
All cancers combined						
No	83	194	1	97	205	1
Yes	33	35	2.20 (1.28, 3.78)	25	37	1.43 (0.81, 2.51)
Esophagus						
No	107	220	1	115	237	1
Yes	9	9	2.06 (0.79, 5.33)	10	7	2.89 (0.90, 9.29)
Stomach						
No	108	216	1	113	235	1
Yes	8	13	1.23 (0.50, 3.06)	7	10	2.67 (0.97, 7.36)
Trachea, bronchus, and lung						
No	106	224	1	118	233	1
Yes	10	5	4.23 (1.41, 12.67)	4	9	0.88 (0.27, 2.91)

cancer was associated with an increased risk of prostate cancer (OR = 2.39, 95% CI: 1.15–5.00). Furthermore, when family history was examined in different types of first-degree relatives (parents, siblings, offspring), excess risk of prostate cancer was seen for those whose father or mother had been diagnosed with esophageal cancer (Table 2). Nonsignificant excess risks were associated with a family history of cancers of the stomach (OR = 1.72, 95% CI: 0.88–3.35), lung (OR = 2.03, 95% CI: 0.95–4.33), female breast (OR = 2.04, 95% CI: 0.75–5.51), and rectum (OR = 2.54, 95% CI: 0.67–9.55).

Family history of the most common tumors (stomach, esophagus, lung) was examined according to the case's age at prostate cancer diagnosis (Table 3). We used the mean age (72 y) of the study subjects as the cut-point. Among those who were diagnosed with prostate cancer before age 72 y, significant excess risks were associated with a family history of any cancer (OR = 2.20, 95% CI: 1.28–3.78) and of lung cancer (OR = 4.23, 95% CI: 1.41–12.67). However, in neither age group was a family history of cancer of the esophagus or stomach significantly associated with excess risk.

Discussion

In this population-based case–control study of prostate cancer in Shanghai, China, none of the study subjects reported a family history of this tumor, due to its low incidence in this population. However, we found that men with a family history of any form of cancer had a significant 1.8-fold risk of prostate cancer. Most pronounced was the significant 2.4-fold risk associated with a family history of esophageal cancer. Excess prostate cancer risk was also associated with a family history of cancers of the lung, stomach, female breast, and rectum, although the increases in risk were not statistically significant. Previous studies, conducted mainly in Western populations, have consistently shown a familial tendency to prostate cancer,[6–9,22] with some studies also suggesting familial aggregation of prostate cancer with malignancies of the breast,[10,14] kidney,[11] stomach,[12,13] ovary,[22] and colorectum.[15,16] Our study provides additional evidence that prostate cancer may be associated with a family history of other malignancies, although an association with esophageal cancer has not been reported previously.

The absence of a familial tendency to prostate cancer in Shanghai suggests that genetic factors may not play a prominent role when the tumors occur in low-risk populations. In Western countries, where the incidence of prostate cancer is nearly 50 times higher than in China, the reported prevalence of a family history of prostate cancer among controls ranges from 5 to 10%.[6,7] Given this figure, the expected prevalence of a family history of prostate cancer would be around 0.1% among the 471 population controls in Shanghai. With such a low prevalence of familial occurrence, our study had very limited statistical power. Even if the familial risk of prostate cancer was five-fold in Shanghai, we would need over 3000 cases and an equal number of controls to detect that level of risk.

Few studies have reported familial aggregation of prostate cancer along with tumors of the digestive tract. As esophageal cancer is relatively common in China, we had sufficient power to detect a familial association with prostate cancer risk. Such an association would be difficult to detect in western populations due to the much lower incidence of esophageal cancer (less than 5/100 000 person-years among US whites). Although we lacked histologic data on esophageal cancer among family members, it is likely that most had squamous cell carcinomas, the predominant cell type in Shanghai.[23] If the link between cancers of the esophagus and the prostate is confirmed, it suggests that certain environmental or genetic determinants of both tumors are shared among family members. In general, low intake of fresh fruits and vegetables has been related to increased risk of both esophageal cancer[24,25] and prostate cancer,[26] and high risk of esophageal squamous cell carcinoma has been inconsistently related to the consumption of moldy food and pickled vegetables in the Chinese population.[27,28] Little is known regarding why a low prostate cancer risk is observed in the Chinese, who have a high esophageal cancer risk from the dietary perspective. Except for deficiency of certain micronutrients such as selenium,[29,30] the lifestyle and environment factors identified for these tumors appear quite different.

An effect of genetic factors is suggested by a case–control study of esophageal cancer in Linxian, China, which revealed an association with the Ser326Cys polymorphism of the DNA repair gene *h*OGG1(human 8-OH-Gua glycosylase/apurinic lyase),[31] a genetic variant also related to prostate cancer risk in Western populations.[32] In a recent study using African Americans, the polymorphic triplet repeat $(GGC)_n$ in the androgen receptor gene has been reported to be associated with increased risk of esophageal cancer, as in prostate cancer.[33] Further studies are needed to clarify the potential role of the genes involved in DNA repair, hormonal pathway, as well as carcinogen or nutrient metabolisms, inflammation, or apoptosis, which might underlie the familial patterns of prostate and other tumors.

Limitations of our study included the following: (1) the relatively small number of cases of prostate cancer in this low-risk area, resulting in limited power to evaluate familial aggregation of this tumor; (2) possible misclassification of family cancer history, since the information was based on self-reports only; (3) differences in recall of family history between cases and controls, although families in China are typically small and close knit; and (4) difficulty in excluding the possibility of chance associations with other tumors due to multiple comparisons.[34]

In summary, our population-based case–control study of prostate cancer in Shanghai, a low-incidence area, revealed an excess risk among men with a family history of esophageal cancer and possibly stomach, lung, and breast cancers. These findings, along with the familial patterns described in high-incidence Western populations, suggest that risk factors for prostate cancer, including genetic predisposition, may be shared by certain other cancers. Further studies of prostate cancer in low- and high-risk populations are needed to clarify the familial association with other tumors, and identify the underlying biological mechanisms.

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